Remarks

Claims 46-50, 55 and 57-86 are pending in the subject application. By this Amendment, Applicants have amended claim 71. Support for the amendment can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 46-50, 55 and 57-86 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claim 71 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action indicates that claim 71 incorrectly depends from claim 67 and should depend from claim 70. By this Amendment, claim 71 has been amended to depend from claim 70. Applicants respectfully assert that the claims as filed are definite. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 46-50, 55 and 57-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for treating a fibrotic disease comprising administering to a patient having a fibrotic disease a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a polypeptide comprising SEQ ID NO:2, wherein said fibrotic disease is lung fibrosis or liver fibrosis, does not reasonably provide enablement for a method for treating a fibrotic disease comprising administering to a patient having a fibrotic disease a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a polypeptide comprising SEQ ID NO:5 or SEQ ID NO:7, wherein said fibrotic disease is lung fibrosis or liver fibrosis. Applicants respectfully assert that the claims as filed are enabled.

While acknowledging that the as-filed specification enables the use of a polypeptide comprising SEQ ID NO:2 for the treatment of a fibrotic disease, the Office Action rejects the pending claims on the basis that "*the specification fails to teach how to treat a fibrotic disease in vivo using fragments and/or mutants of full length INSP035*" (page 5, lines 9-11). The Office Action also argues that because SEQ ID NOs: 5 and 7 contain one-half the number of amino acid residues as SEQ ID NO: 2, "*it is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed*" (page 5, lines 20-22). The Office Action concludes that "*undue burden would be required of the skilled*

artisan to make and/or use the claimed invention in its full scope" (page 7, lines 4-5). Applicants respectfully disagree and traverse the rejection of record.

At the outset, Applicants note that the pending claims do not recite fragments and/or mutants of INSP035 full length (corresponding to SEQ ID NO:2) nor polypeptides having random mutations or deletions. Rather, the claims recite polypeptides comprising or consisting of SEQ ID NOs. 5 or 7, *i.e.* polypeptides comprising or consisting of definite sequences, shown to display similar activity as SEQ ID NO:2 on TRAIL inhibition *in vitro* (see page 7, lines 18-22 and page 27 line 7). It is further noted that Example 5 of the present invention describes an assay for testing the activity of INSP035 in bleomycin treated mice (a mice model of lung fibrosis).

Applicants submit that the as-filed specification fully enables the claimed invention. For example, polyhistidine labeled forms of SEQ ID NOs: 2, 5 and 7 have been demonstrated to inhibit TRAIL activity (see Figure 1 and the discussion of Figure 1 at page 7, lines 18-22). In that passage, it is stated that "INSP035-His Modified Medium Long Form (SEQ ID NO: 8) in TRAIL assay. Y-axis represents the percentage of TRAIL inhibition. X-axis represents the log dilution of the modified medium form of INSP035. **Similar curves were obtained with SEQ ID NO: 3 (INSP035-His Long Form) and SEQ ID NO: 6 (INSP035-His Medium Form)**" (emphasis added). The as-filed specification teaches that SEQ ID NOs: 3, 6 and 8 are polyhistidine labeled forms of SEQ ID NOs: 2, 5 and 7 (see the as-filed specification at page 8, lines 24-26). Thus, the as-filed specification provides evidence that the claimed polypeptides are capable of inhibiting TRAIL activity.

The Office Action cites two documents supporting the argument that a variant/mutant of a protein may display similar *in vitro* activity as the full-length protein, but lack *in vivo* activity. However, Applicants note that the art also recognizes that shorter polypeptides (variants/mutants) retain both *in vivo* and *in vitro* activity. For example, parathyroid hormone (PTH) is a polypeptide comprising 84 residues, known to induce anabolic effects on bone. An N-terminal fragment of PTH, the peptide PTH(1-34), although containing fewer than one-half the number of amino acid residues as PTH, displays similar *in vivo* effect as compared to PTH. This is confirmed by the fact that both polypeptides PTH and PTH(1-34) are registered drugs (*e.g.*, PREOTACT and FORTEO) for the treatment or postmenopausal women with osteoporosis (copies of the product inserts for these drugs

are attached to the response for the convenience of the Examiner). The second example, leptin, is a polypeptide consisting of 167 residues (the mature form consists of 147 residues). It is well-known for reducing body weight and food intake *in vivo* (see Table 1, page 16 of WO97/46585). Similar *in vivo* effects were shown for a leptin fragment comprising 15 residues (residues 116-130 of leptin). This fragment contained fewer than 10% of the amino acid residues found in full length leptin yet exerted similar biologic effects (see Table 7, page 72 and Figure 4J of WO00/11173). Thus, it is respectfully submitted that the as-filed specification fully enables the claimed invention and that undue experimentation would not be required in order to practice the claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Gainesville, FL 32614-2950

FCE/jb
Attachments: Product insert for PREOTACT
Product insert for FORTEO

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THEMEDICINAL PRODUCT

Preotact 100 micrograms powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Preotact contains parathyroid hormone manufactured using a strain of Escherichia coli modified by recombinant DNA technology.

The medicinal product is supplied in a dual-chamber cartridge.

The first chamber contains 1.61 mg parathyroid hormone.

Each dose of 71.4 microliter contains 100 micrograms parathyroid hormone. Each cartridge contains 14 doses.

The second chamber contains a sterile solvent for reconstitution.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White to off-white powder and clear, colourless solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at high risk of fractures (see section 5.1).

A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.

4.2 Posology and method of administration

The recommended dose is 100 micrograms of parathyroid hormone administered once-daily as a subcutaneous injection into the abdomen.

Patients must be trained to use the proper injection techniques (see section 6.6). A user manual is available with the Preotact pen to instruct patients on the correct use of the pen. The pen is not included in the packs with cartridges.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

Data support continuous treatment with Preotact for up to 24 months (see section 4.4).

Following treatment with Preotact patients can be treated with a bisphosphonate to further increase bone mineral density (see section 5.1).

Specific populations

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 ml/min). There is no data available in patients with severe renal impairment. Preotact should therefore not be used in patients with severe renal impairment (see section 4.3).

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment (total score of 7 to 9 on the Child-Pugh scale). There is no data available in patients with severe hepatic impairment. Preotact should therefore not be used in patients with severe hepatic impairment (see section 4.3).

Children and adolescents

The safety and efficacy of Preotact in patients under 18 years have not been studied. Preotact should not be used in paediatric patients or young adults.

Elderly

Dose adjustment based upon age is not required (see section 5.2).

4.3 Contraindications

Preotact is contraindicated in patients

- with hypersensitivity to parathyroid hormone or to any of the excipients (see section 6.1)
- who have previously received radiation therapy to the skeleton
- with pre-existing hypercalcemia and other disturbances in the phosphocalcic metabolism
- with metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone)
- with unexplained elevations of bone-specific alkaline phosphatase
- with severe renal impairment
- with severe hepatic impairment

4.4 Special warnings and precautions for use

Patients initiated on Preotact therapy should be monitored at months 1, 3 and 6 for elevated levels of serum and/or urinary calcium. Monitoring beyond 6 months is not recommended for patients whose total serum calcium is within the normal limits at 6 months.

Elevated serum calcium was observed during Preotact treatment. Serum calcium concentrations reach a maximum between 6 and 8 hours post dose and normally return to baseline by 20 to 24 hours after each administration of parathyroid hormone. Therefore if any blood samples are taken from a patient for monitoring of calcium levels, this should be done at least 20 hours after the most recent injection.

Management of elevated serum calcium

Patients with persistent elevated serum calcium (above the upper normal level) should be evaluated for underlying disease (e.g. hyperparathyroidism). If no underlying condition is found, the following management procedures should be followed:

- Calcium and vitamin D supplementation should be withdrawn
- The frequency of Preotact dosing should be changed to 100 micrograms every other day
- If elevated levels continue, Preotact therapy should be stopped and the patient monitored until the abnormal values have reverted to normal

Patients with pre-existing hypercalcemia and/or hypercalciuria

Preotact has been studied in patients with pre-existing hypercalcemia and/or hypercalciuria. In these patients, Preotact treatment was more likely to exacerbate their underlying hypercalcemia and/or hypercalciuria.

Preotact has not been studied in patients with active urolithiasis. Preotact should be used with caution in patients with active or previous urolithiasis.

Caution should be exercised in patients receiving cardiac glucosides (see section 4.5).

Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of Preotact (see section 5.3). The occurrence of osteosarcoma only occurred at doses that produced systemic exposures $\geq$ 27-times higher than that observed in humans at the 100 micrograms dose. Until further clinical data becomes available the recommended treatment time of 24 months should not be exceeded.

Preotact contains metacresol, which may cause allergic reactions.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

4.5 Interaction with other medicinal products and other forms of interaction

Parathyroid hormone is a natural peptide that is not metabolised by, and does not inhibit hepatic microsomal drug-metabolising enzymes (e.g. cytochrome P450 isoenzymes). Furthermore, parathyroid hormone is not protein bound and has a low volume of distribution. Consequently, no interaction with other medicinal products would be anticipated and no specific drug-drug interactions studies were performed. No potential for drug interactions was identified in the clinical program.

Combining parathyroid hormone with alendronate use has not been shown to provide any advantage over either form of treatment alone, when the end point of bone mineral density was evaluated. (see section 5.1).

From the knowledge of the mechanism of action, combined use of Preotact and cardiac glucosides may predispose patients to digitalis toxicity if hypercalcemia develops.

4.6 Pregnancy and lactation

There are no data available from the use of parathyroid hormone during pregnancy and lactation. Animal studies of reproductive toxicity are incomplete (see section 5.3).

Parathyroid hormone should not be used during pregnancy or breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As some episodes of dizziness have been described in patients treated with Preotact, patients should refrain from driving or using machines until symptoms have subsided.

4.8 Undesirable effects

The following adverse reaction (ADR) data are based on two placebo-controlled studies involving 2642 postmenopausal osteoporotic women of whom 1341 received parathyroid hormone. Approximately 71.4 % of the patients on parathyroid hormone reported at least one ADR.

Hypercalcemia and/or hypercalciuria reflect the known pharmacodynamic actions of parathyroid hormone in the gastrointestinal tract, the kidney, and the bone. Hypercalcemia was reported in 25.3 % of patients and hypercalciuria in 39.3 % of patients treated with Preotact. Hypercalcemia was transient and was reported most frequently in the first 3 months of treatment. It was managed during the clinical programme by monitoring laboratory values and the use of a pre-specified management algorithm (see sections 4.3, 4.4, and 5.1).

The only other very commonly reported ADR was nausea.

The table below gives an overview of the ADRs where the incidence is at least 0.5 % higher in the parathyroid hormone group compared to placebo. The following categories are used to rank the undesirable effects by frequency of occurrence: very common (> 1/10); common (> 1/100 and <1/10); uncommon (> 1/1000 and <1/100); rare (> 1/10,000 and <1/1000); and very rare (<1/10,000), including isolated reports.

System organ class	**PTH N=1341 (%)**
Infections and Infestations	
Uncommon	
Influenza	0.5
Metabolism and nutrition disorders	
Very common	
Hypercalcemia	25.3
Common	
Blood calcium increased	3.1
Uncommon	
Blood alkaline phosphatase increased	0.8
Anorexia	0.6
Blood uric acid increased	0.6
Nervous system disorders	
Common	
Headache	9.3
Dizziness	3.9
Uncommon	
Dysgeusia	0.8
Parosmia	0.7
Cardiac disorders	
Common	
Palpitations	1.0
Gastrointestinal disorders	
Very common	
Nausea	13.5
Common	
Vomiting	2.5
Constipation	1.8
Dyspepsia	1.3
Diarrhoea	1.0
Uncommon	
Abdominal pain	0.8
Musculoskeletal, connective tissue and bone disorders	
Common	
Muscle cramp	1.1
Pain in extremity	1.1
Back pain	1.0
Renal and urinary disorders	

Very common	
Hypercalciuria	39.3
Common	
Urine calcium/creatinine ratio increased	2.9
Urine calcium increased	2.2

General disorders and administration site conditions	
Common	
Injection site erythema	2.6
Fatigue	1.8
Asthenia	1.2
Uncommon	
Injection site irritation	0.9

Preotact increases serum uric acid concentrations. For all subjects who received parathyroid hormone 100 micrograms blood uric acid increase was reported for 8 subjects (0.6 %) and hyperuricemia was reported for 5 subjects (0.4 %). Although gout, arthralgia and nephrolithiasis were reported as ADRs, the relationship to elevations in uric acid due to Preotact administration has not been fully established.

Antibodies to parathyroid hormone
In a large phase III clinical study, antibodies to parathyroid hormone were detected in 3 % of women receiving Preotact compared to 0.2 % of women receiving placebo. In these women with a positive titer, there was no evidence of hypersensitivity reactions, allergic reactions, effects on bone mineral density response, or effects on serum calcium.

4.9 Overdose

Signs and symptoms
In the Preotact clinical program, accidental overdose was reported for 17 subjects.

Preotact has been administered in single doses up to 5 micrograms/kg and in repeated doses of up to 3 micrograms/kg/day for 3 days and up to 2.5 micrograms/kg/day for 7 days. The effects of overdose that might be expected include delayed hypercalcemia, nausea, vomiting, dizziness and headache.

Overdose management
There is no specific antidote for Preotact. Treatment of suspected overdose should include temporary discontinuation of Preotact, monitoring of serum calcium, and implementation of appropriate, supportive measures, such as hydration. Due to the relatively short duration of the pharmacological activity of Preotact further measures should not be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: parathyroid hormone, ATC code: H05 AA03.

Mechanism of action
Preotact contains recombinant human parathyroid hormone which is identical to the full-length native 84-amino acid polypeptide.

Physiological actions of parathyroid hormone include stimulation of bone formation by direct effects on bone forming cells (osteoblasts) indirectly increasing the intestinal absorption of calcium and increasing the tubular reabsorption of calcium and excretion of phosphate by the kidney.

Pharmacodynamic effects

The skeletal effects of parathyroid hormone depend upon the pattern of systemic exposure. Transient elevations in parathyroid hormone levels after subcutaneous injection of Preotact stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity.

Effects on serum calcium concentrations
Parathyroid hormone is the principal regulator of serum calcium homeostasis. In response to subcutaneous doses of Preotact (100 micrograms parathyroid hormone), serum total calcium levels increase gradually and reach peak concentration (mean increase in 129 patients, 0.15 mmol/l) at approximately 6 to 8 hours after dosing. In general, serum calcium levels return to baseline levels 24 hours after dosing.

Based on two placebo-controlled studies involving 2642 postmenopausal osteoporotic women, hypercalcemia was reported in 25.3 % of patients treated with Preotact compared to 4.3 % of placebo-treated patients. The hypercalcemia was transient and was reported most frequently in the first 3 months of treatment. It was managed during the clinical programme by monitoring laboratory values and the use of a pre-specified management algorithm.(see sections 4.3 and 4.4).

Clinical efficacy
Effect on fracture incidence
The pivotal study was an 18-month double-blind, placebo-controlled, phase III study (TOP) of the effect of Preotact on fracture incidence in women with postmenopausal osteoporosis.

A total of 2532 patients (1286 Preotact and 1246 placebo), aged 45-94 years (8.1 % 45-54 years and 11.4 % $\geq$ 75 years), were randomised to receive 100 micrograms/day or placebo with daily calcium (700 mg) and vitamin D (400 IU) supplementation.

Overall, approximately 19 % of the subjects in each treatment group had at least 1 prevalent vertebral fracture at baseline. The mean baseline lumbar T score was approximately -3.0 in each treatment group.

Of the 2532 randomised intention-to-treat (ITT) patients, a total of 59 patients experienced at least one new vertebral fracture, placebo: 42 (3.37 %) – Preotact: 17 (1.32 %), p=0.001. Patients in the Preotact treatment group had a 61 % relative risk reduction of a new vertebral fracture at month 18 compared to the patients in the placebo group.

To prevent one or more new vertebral fractures, 48 women had to be treated for a median of 18 months for the total population. For patients with pre-existing fractures, number needed to treat (NNT) is 21 patients.

There was no significant difference between the treatment groups in the incidence of any non-vertebral clinical fracture: 5.52 % for Preotact vs. 5.86 % for placebo.

The most relevant fracture reduction was observed among patients at high risk of fractures such as patients with previous fractures and in patients with a lumbar spine T-score of $\leq$ - 3.

Relatively few patients less than 5 years postmenopausal and 45-54 years of age were enrolled in the phase III study (2-3 %). The results for these subjects were not different from the results in the study as a whole.

Effect on bone mineral density (BMD)
In the pivotal study, Preotact increased BMD in the lumbar spine after 18 months treatment by 6.5 % compared with -0.3 % for placebo ($p<0.001$). Significant increases in hip BMD (total, femoral neck, trochanter) were observed at study endpoint; 1.0, 1.8 and 1.0 %, respectively, for Preotact versus -1.1, -0.7 and -0.6 % for placebo ($p<0.001$).

Continued treatment for up to 24 months in an open-label extension of this study resulted in a continued increase in BMD. The increase from baseline in lumbar spine and femoral neck BMD was 6.8 % and 2.2 %, respectively in patients treated with Preotact.

The effects of Preotact on bone architecture were evaluated using quantitative computed tomography (QCT) and peripheral QCT. Volumetric trabecular BMD at the lumbar spine increased by 38 % over baseline at 18 months. Similarly, volumetric trabecular BMD at the total hip increased by 4.7 %. Similar increases occurred at the femoral neck, trochanter, and intertrochanter. Treatment with Preotact reduced volumetric cortical bone BMD (measured at the distal radius and mid-shaft tibia), while periosteal circumference or indices of cortical bone strength were maintained.

In the 24-month alendronate combination therapy study (PaTH), the effects of Preotact on bone architecture were also evaluated using QCT. Volumetric trabecular BMD at the lumbar spine increased by 26, 13, and 11 % (Preotact, Preotact and alendronate and alendronate, respectively) over baseline at 12 months. Similarly, volumetric trabecular BMD at the total hip increased by 9, 6, and 2 %, respectively, in the 3 groups.

Treatment of osteoporosis with combination and sequential therapy
The PaTH study was a NIH sponsored randomised, placebo-controlled, 2 year, multicenter, double-blind trial of Preotact and alendronate as monotherapy and in combination for the treatment of postmenopausal osteoporosis. Inclusion criterias were; women between 55 and 85 years of age with BMD T-scores below -2.5 or below -2 and at least one additional risk factor for fracture. All women were given calcium (400-500 mg) and vitamin D (400 IU) supplements.

A total of 238 postmenopausal women, were randomly assigned to one of the following treatment groups; Preotact (100 micrograms parathyroid hormone), alendronate (10 mg), or the combination of both, and followed for 12 months. In the second year of the study women in the original Preotact group were randomly assigned to receive either alendronate or matching placebo, and women in the other two groups received alendronate.

At baseline a total of 165 women (69 %) had a T-score below –2.5, and 112 (47 %) reported at least one fracture after menopause.

One year of therapy, showed the following results: The increases in lumbar spine BMD above baseline were similar in the Preotact and combination-therapy groups (6.3 and 6.1 %, respectively), but were somewhat smaller in the alendronate group (4.6 %). Increases in BMD at the total hip were 0.3, 1.9, and 3.0 % for the 3 groups, respectively.

At the end of year 2 (12 months after Preotact was discontinued), there was a 12.1 % mean increase in dual energy X-ray absorptiometry (DXA) spine BMD for patients who received alendronate for the second year. For the patients who received placebo during the second year, the mean percent increase was 4.1 % compared to baseline, but had decreased slightly compared to the end of 12 months of Preotact treatment. For the mean change in hip BMD, there was a 4.5 % increase from baseline with one year of alendronate compared to a 0.1 % decrease after one year of placebo.

Preotact in combination with hormone replacement therapy (HRT) in 180 postmenopausal women has been shown to significantly increase lumbar spine BMD at 12 months compared with HRT alone (7.1 % vs. 1.1 %, $p<0.001$). The combination was effective regardless of age, baseline rate of bone turnover, or baseline BMD.

5.2 Pharmacokinetic properties

Absorption
Subcutaneous administration of 100 micrograms of parathyroid hormone into the abdomen produces a rapid increase in plasma parathyroid hormone levels and achieves a peak at 1 to 2 hours after dosing.

The average half-life is of about 1.5 hours. The absolute bioavailability of 100 micrograms of parathyroid hormone after subcutaneous administration in the abdomen is 55 %.

Distribution
The volume of distribution at steady-state following intravenous administration is approximately 5.4 l. Intersubject variability in the volume of distribution of parathyroid hormone is about 40 %.

Biotransformation
Parathyroid hormone is efficiently removed from the blood by a receptor-mediated process in the liver and is broken down into smaller peptide fragments. The fragments derived from the amino-terminus are further degraded within the cell while the fragments derived from the carboxy-terminius are released back into the blood and cleared by the kidney. These carboxy-terminal fragments are thought to play a role in the regulation of parathyroid hormone activity. Under normal physiologic conditions, full-length parathyroid hormone (1-84) constitutes only 5-30 % of the circulating forms of the molecule, while 70-95 % is present as carboxy-terminal fragments. Following a subcutaneous dose of Preotact, C-terminal fragments make up about 60-90% of the circulating forms of the molecule. Systemic clearance of parathyroid hormone (45.3 l/hour) following an intravenous dose is close to normal liver plasma flow and is consistent with extensive hepatic metabolism of the active substance. Intersubject variability in systemic clearance is about 15 %.

Elimination
Parathyroid hormone is metabolised in the liver and to a lesser degree in the kidney. Parathyroid hormone is not excreted from the body in its intact form. Circulating carboxy-terminal fragments are filtered by the kidney, but are subsequently broken to even smaller fragments during tubular reuptake.

Hepatic impairment
There was a modest increase of about 20 % in the mean baseline corrected exposure (AUC) to parathyroid hormone in a study conducted in 6 men and 6 women with moderate hepatic impairment as compared with a matched group of 12 subjects with normal hepatic function.

No studies have been conducted in patients with severe hepatic impairment.

Renal impairment
The overall exposure and C_{max} of parathyroid hormone were slightly increased (22 % and 56 %, respectively) in a group of 8 male and 8 female subjects with mild-to-moderate renal impairment (creatinine clearances of 30 to 80 ml/min) compared with a matched group of 16 subjects with normal renal function.

The pharmacokinetics of parathyroid hormone in patients with severe renal impairment (creatinine clearance of less than 30 ml/min) has not been investigated.

Elderly
No differences in Preotact pharmacokinetics were detected with regard to age (range 47-88 years). Dosage adjustment based on age is not required.

Gender
The medicinal product has only been studied in postmenopausal women.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, mutagenicity, toxicity to fertility and general reproduction, and local tolerance.

In monkeys receiving daily subcutaneous doses for 6 months, there was an increased occurrence of renal tubular mineralization at exposure levels below clinical exposure levels.

Rats treated with near life-time daily injections had dose-dependent exaggerated bone formation and an increased incidence of bone tumours, including osteosarcoma, most probably due to an epigenetic mechanism. Due to the differences in bone physiology in rats and humans, the clinical relevance of these findings is probably minor. No osteosarcomas have been observed in clinical trials.

There are no studies of foetal, developmental, perinatal or postnatal toxicity. It is unknown whether recombinant human parathyroid hormone is excreted in the milk of lactating animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol
Citric acid monohydrate
Sodium chloride
Hydrochloric acid, dilute (for pH adjustment)
Sodium hydroxide 1N (for pH adjustment)

Solvent
Metacresol
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder: 30 months

Mixed solution: chemical and physical in-use stability has been demonstrated for 28 days at 2-8°C. During the 28-day period the mixed solution can be stored for up to 7 days at temperatures below 25°C.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

Mixed solution: Store in a refrigerator (2-8°C). Do not freeze. Once the cartridge is mixed it can be stored outside the refrigerator at temperatures below 25°C for up to 7 days during the 28 day use period.(see section 6.3).

6.5 Nature and contents of container

The container closure system is comprised of a dual-chamber cartridge, a center stopper, a crimp cap (containing a rubber seal) sealing the first chamber containing lyophilised powder and an end stopper sealing the second chamber containing the solvent for mixing.

Cartridge: The glass of the dual-chamber cartridge is made of glass Type I.

Stopper (center and end): The stopper is made of bromobutyl rubber, grey.

Crimp cap (containing a rubber seal): The crimp cap is made of aluminium and the rubber seal is made of bromobutyl rubber.

Each dual-chamber cartridge contains 1.61 mg parathyroid hormone and 1.13 ml solvent (14 doses).

Preotact is available in packs of 2 and 6 cartridges. Not all pack sizes may be marketed.

The Preotact pen and needles are not included.

6.6 Special precautions for disposal

Preotact is injected using the re-usable pen, Preotact pen. The contents of the dual-chamber cartridge is mixed in the Preotact pen. After mixing the liquid should be clear and colourless.

DO NOT SHAKE; shaking may cause denaturation of the active substance.

If the mixed solution is cloudy, coloured or contains particles the cartridge should be removed from the Preotact pen and a new cartridge inserted.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Nycomed Danmark ApS
Langebjerg 1
DK-4000 Roskilde
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FORTEO safely and effectively. See full prescribing information for FORTEO.

FORTEO (teriparatide [rDNA origin] injection) for subcutaneous use
Initial U.S. Approval: 2002

WARNING: POTENTIAL RISK OF OSTEOSARCOMA
See full prescribing information for complete boxed warning.

- **In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor. (5.1, 13.1)**
- **Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk. (5.1)**
- **FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (e.g., those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton). (5.1)**

RECENT MAJOR CHANGES

Indications and Usage, Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis (1.3)	07/2009
Dosage and Administration, Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis (2.3)	07/2009

INDICATIONS AND USAGE

FORTEO is recombinant human parathyroid hormone analog (1-34), [rhPTH(1-34)] indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture (1.2)
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture (1.3)

DOSAGE AND ADMINISTRATION

- Recommended dose is 20 mcg subcutaneously once a day (2.1, 2.2, 2.3)
- Administer as a subcutaneous injection into the thigh or abdominal wall (2.4)
- Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (2.4)
- Use of the drug for more than 2 years during a patient's lifetime is not recommended (2.5)

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)

CONTRAINDICATIONS

- Patients with hypersensitivity to teriparatide or to any of its excipients (4)

WARNINGS AND PRECAUTIONS

- Patients with Paget's disease of bone, pediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton: Should not be treated with FORTEO (5.1, 8.4)
- Treatment duration: Use of FORTEO for more than 2 years during a patient's lifetime is not recommended. (5.2)
- Patients with bone metastases, history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders: Should not be treated with FORTEO (5.3, 5.4, 5.5)
- Laboratory alterations: FORTEO may increase serum calcium, urinary calcium, and serum uric acid (5.5, 5.6)
- Urolithiasis: Use with caution in patients with active or recent urolithiasis because of risk of exacerbation (5.6)
- Orthostatic hypotension: Transient orthostatic hypotension may occur with initial doses of FORTEO (5.7)

ADVERSE REACTIONS

Most common adverse reactions (>10%) include: arthralgia, pain, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Digoxin: Use FORTEO with caution in patients receiving digoxin. Transient hypercalcemia may predispose patients to digitalis toxicity (5.8, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue nursing or FORTEO, taking into account the importance of treatment to the mother (8.3)
- Pediatric Use: FORTEO should not be used in pediatric and young adult patients with open epiphyses due to increased baseline risk of osteosarcoma (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) ***[see Warnings and Precautions (5.1), Adverse Reactions (6.2), and Nonclinical Toxicology (13.1)].***

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

FORTEO is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, FORTEO reduces the risk of vertebral and nonvertebral fractures *[see Clinical Studies (14.1)]*.

1.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture

FORTEO is indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy *[see Clinical Studies (14.2)]*.

1.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

FORTEO is indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.4 Administration

- FORTEO should be administered as a subcutaneous injection into the thigh or abdominal wall. There are no data available on the safety or efficacy of intravenous or intramuscular injection of FORTEO.
- FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur *[see Warnings and Precautions (5.7)]*.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. FORTEO is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored.
- Patients and caregivers who administer FORTEO should receive appropriate training and instruction on the proper use of the FORTEO delivery device from a qualified health professional *[see Patient Counseling Information (17.5)]*.

2.5 Treatment Duration

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patient's lifetime is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

4 CONTRAINDICATIONS

Do not use FORTEO in patients with:

- Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Osteosarcoma

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration *[see Boxed Warning and Nonclinical Toxicology (13.1)]*. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma.

These include:

- Paget's disease of bone. Unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone.
- Pediatric and young adult patients with open epiphyses.
- Prior external beam or implant radiation therapy involving the skeleton.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org

5.2 Treatment Duration

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended.

5.3 Bone Metastases and Skeletal Malignancies

Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO.

5.4 Metabolic Bone Diseases

Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO.

5.5 Hypercalcemia and Hypercalcemic Disorders

FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO.

5.6 Urolithiasis or Pre-existing Hypercalciuria

In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

5.7 Orthostatic Hypotension

FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

5.8 Drug Interactions

Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Treatment of Osteoporosis in Men and Postmenopausal Women

The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day.

The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients.

Table 1 lists adverse events from the two principal osteoporosis trials in men and postmenopausal women that occurred in ≥2% of FORTEO-treated and more frequently than placebo-treated patients.

Table 1. Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality

	FORTEO N=691	**Placebo** N=691
Event Classification	**(%)**	**(%)**
Body as a Whole		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck pain	3.0	2.7
Cardiovascular		
Hypertension	7.1	6.8
Angina pectoris	2.5	1.6
Syncope	2.6	1.4
Digestive System		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhea	5.1	4.6
Dyspepsia	5.2	4.1
Vomiting	3.0	2.3
Gastrointestinal disorder	2.3	2.0
Tooth disorder	2.0	1.3
Musculoskeletal		
Arthralgia	10.1	8.4
Leg cramps	2.6	1.3
Nervous System		
Dizziness	8.0	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
Respiratory System		
Rhinitis	9.6	8.8
Cough increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
Skin and Appendages		

Rash	4.9	4.5
Sweating	2.2	1.7

Immunogenicity — In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

Laboratory Findings

Serum Calcium — FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

Urinary Calcium — FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo *[see Clinical Pharmacology (12.2)]*.

Serum Uric Acid — FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

Renal Function — No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment.

Studies in Men and Women with Glucocorticoid-Induced Osteoporosis

The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control).

Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Osteosarcoma: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing [*see Warnings and Precautions (5.1)*]
- Hypercalcemia: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following:

- Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria
- Investigations: Hyperuricemia
- Respiratory System: Acute dyspnea, chest pain
- Musculoskeletal: Muscle spasms of the leg or back
- Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema

7 DRUG INTERACTIONS

7.1 Digoxin

A single FORTEO dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect). However, because FORTEO may transiently

increase serum calcium, FORTEO should be used with caution in patients taking digoxin *[see Warnings and Precaution (5.8) and Clinical Pharmacology (12.3)]*.

7.2 Hydrochlorothiazide

The coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied *[see Clinical Pharmacology (12.3)]*.

7.3 Furosemide

Coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg in healthy people and patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C — There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥120 times the human dose (based on surface area, mcg/m^2). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

Exposure multiples were normalized based on body surface area (mcg/m^2). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day).

8.3 Nursing Mothers

It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No studies have been performed in patients with hepatic impairment. *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea,

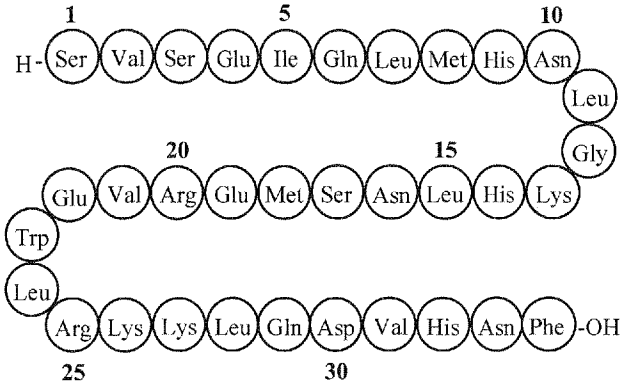
weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

Overdose Management — There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

11 DESCRIPTION

FORTEO (teriparatide [rDNA origin] injection) contains recombinant human parathyroid hormone (1-34), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



Teriparatide (rDNA origin) is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. FORTEO is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable delivery device (pen) for subcutaneous injection. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

Each cartridge, pre-assembled into a delivery device, delivers 20 mcg of teriparatide per dose each day for up to 28 days.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous 84-amino acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

12.2 Pharmacodynamics

Pharmacodynamics in Men and Postmenopausal Women with Osteoporosis

Effects on Mineral Metabolism — Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (e.g., increases serum calcium and decreases serum phosphorus).

Serum Calcium Concentrations — When teriparatide 20 mcg is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16 to 24 hours after each dose.

In a clinical study of postmenopausal women with osteoporosis, the median peak serum calcium concentration measured 4 to 6 hours after dosing with FORTEO (teriparatide 20 mcg) was 2.42 mmol/L (9.68 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in >99% of women at each visit. Sustained hypercalcemia was not observed.

In this study, 11.1% of women treated with FORTEO had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with 1.5% of women treated with placebo. The percentage of women treated with FORTEO whose serum calcium was above the upper limit of normal on consecutive 4- to 6-hour post-dose measurements was 3.0% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or FORTEO doses were reduced. The timing of these dose reductions was at the discretion of the investigator. FORTEO dose adjustments were made at varying intervals after the first observation of increased serum calcium (median 21 weeks). During these intervals, there was no evidence of progressive increases in serum calcium.

In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on serum calcium were similar to those observed in postmenopausal women. The median peak serum calcium concentration measured 4 to 6 hours after dosing with FORTEO was 2.35 mmol/L (9.44 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6.0% of men treated with FORTEO daily had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with none of the men treated with placebo. The percentage of men treated with FORTEO whose serum calcium was above the upper limit of normal on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Although calcium supplements and/or FORTEO doses could have been reduced in these men, only calcium supplementation was reduced *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

In a clinical study of women previously treated for 18 to 39 months with raloxifene (n=26) or alendronate (n=33), mean serum calcium >12 hours after FORTEO injection was increased by 0.09 to 0.14 mmol/L (0.36 to 0.56 mg/dL), after 1 to 6 months of FORTEO treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >2.76 mmol/L (11.0 mg/dL), and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >2.76 mmol/L (11.0 mg/dL). The highest serum calcium reported was 3.12 mmol/L (12.5 mg/dL). None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum calcium were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Urinary Calcium Excretion — In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO increased urinary calcium excretion. The median urinary excretion of calcium was 4.8 mmol/day (190 mg/day) at 6 months and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and 0.3 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the women treated with FORTEO or placebo.

In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These levels were 0.5 mmol/day (20 mg/day) higher and 0.2 mmol/day (8.0 mg/day) lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the men treated with FORTEO or placebo.

Phosphorus and Vitamin D — In single-dose studies, teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (<0.74 mmol/L or 2.4 mg/dL) was not observed in clinical trials with FORTEO.

In clinical trials of daily FORTEO, the median serum concentration of 1,25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men, compared with baseline. In the placebo group, this concentration decreased by 2% in women and increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months was decreased by 19% in women and 10% in men compared with baseline. In the placebo group, this concentration was unchanged in women and increased by 1% in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum phosphorus were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Effects on Markers of Bone Turnover — Daily administration of FORTEO to men and postmenopausal women with osteoporosis in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling.

Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum markers of bone turnover were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

12.3 Pharmacokinetics

Absorption — Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.

Distribution — Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25% to 50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site.

Metabolism and Excretion — No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Pediatric Patients — Pharmacokinetic data in pediatric patients are not available *[see Warnings and Precautions (5.1)]*.

Geriatric Patients — No age-related differences in teriparatide pharmacokinetics were detected (range 31 to 85 years).

Gender — Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dose for both genders is 20 mcg/day.

Race — The populations included in the pharmacokinetic analyses were 98.5% Caucasian. The influence of race has not been determined.

Renal Impairment — No pharmacokinetic differences were identified in 11 patients with mild or moderate renal impairment [creatinine clearance (CrCl) 30 to 72 mL/min] administered a single dose of teriparatide. In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment — No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney *[see Use in Specific Populations (8.6)]*.

Drug Interactions

Digoxin — In a study of 15 healthy people administered digoxin daily to steady state, a single FORTEO dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect). However, sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO may transiently increase serum calcium, FORTEO should be used with caution in patients taking digoxin *[see Drug Interactions (7.1)]*.

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied *[see Drug Interactions (7.2)]*.

Furosemide — In a study of 9 healthy people and 17 patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min), coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important *[see Drug Interactions (7.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in

osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

The relevance of these animal findings to humans is uncertain.

Mutagenesis — Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.

Impairment of Fertility — No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m^2).

13.2 Animal Toxicology

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area, mcg/m^2).

In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The safety and efficacy of once-daily FORTEO, median exposure of 19 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis (FORTEO 20 mcg, n=541).

All women received 1000 mg of calcium and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

Effect on Fracture Incidence

New Vertebral Fractures — FORTEO, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5.0% in the FORTEO group. This difference was statistically significant ($p<0.001$); the absolute reduction in risk was 9.3% and the relative reduction was 65%. FORTEO was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover, or baseline BMD (*see* Table 2).

Table 2. Effect of FORTEO on Risk of Vertebral Fractures in Postmenopausal Women with Osteoporosis

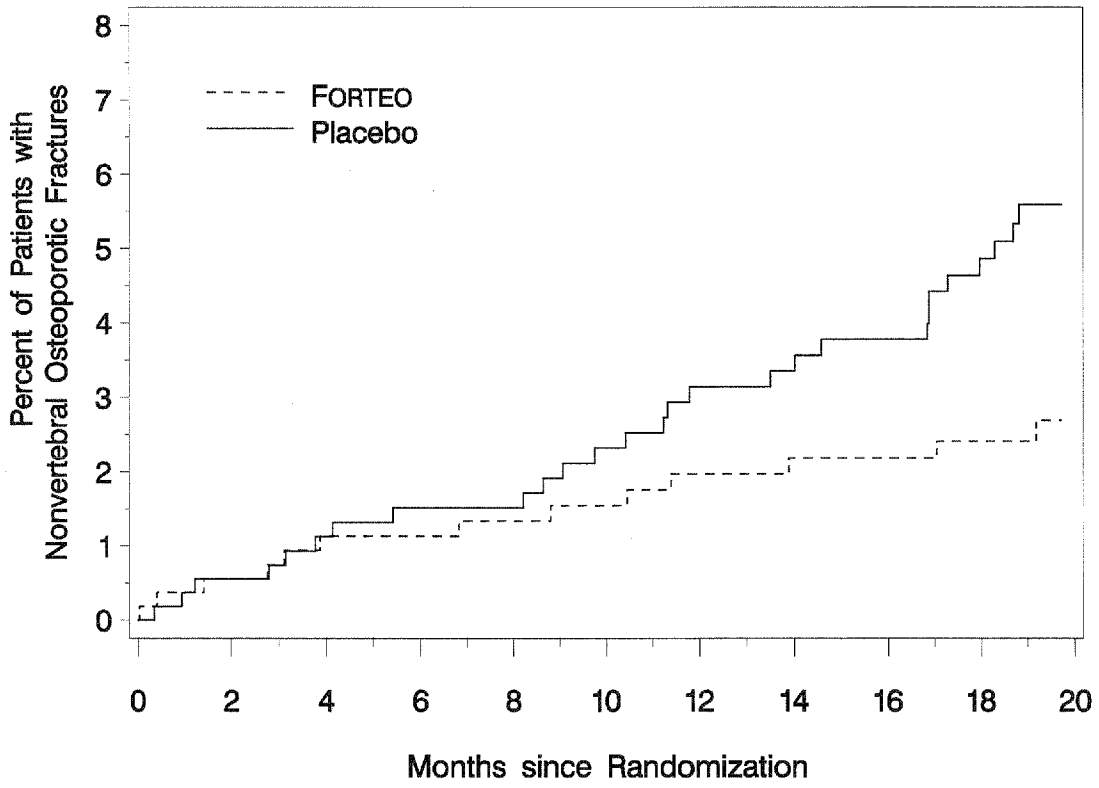
	Percent of Women With Fracture			
	FORTEO (N=444)	**Placebo (N=448)**	**Absolute Risk Reduction (%, 95% CI)**	**Relative Risk Reduction (%, 95% CI)**
New fracture (≥1)	5.0[a]	14.3	9.3 (5.5-13.1)	65 (45-78)
1 fracture	3.8	9.4		
2 fractures	0.9	2.9		
≥3 fractures	0.2	2.0		

[a] $p \leq 0.001$ compared with placebo.

New Nonvertebral Osteoporotic Fractures — FORTEO significantly reduced the risk of any nonvertebral fracture from 5.5% in the placebo group to 2.6% in the FORTEO group ($p<0.05$). The absolute reduction in risk was 2.9% and the relative reduction was 53%. The incidence of new nonvertebral fractures in the FORTEO group compared with the placebo group was ankle/foot (0.2%, 0.7%), hip (0.2%, 0.7%), humerus (0.4%, 0.4%), pelvis (0%, 0.6%), ribs (0.6%, 0.9%), wrist (0.4%, 1.3%), and other sites (1.1%, 1.5%), respectively.

The cumulative percentage of postmenopausal women with osteoporosis who sustained new nonvertebral fractures was lower in women treated with FORTEO than in women treated with placebo (*see* Figure 1).

Figure 1. Cumulative Percentage of Postmenopausal Women with Osteoporosis Sustaining New Nonvertebral Osteoporotic Fractures



Effect on Bone Mineral Density (BMD)

FORTEO increased lumbar spine BMD in postmenopausal women with osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Postmenopausal women with osteoporosis who were treated with FORTEO had statistically significant increases in BMD from baseline to endpoint at the lumbar spine, femoral neck, total hip, and total body (*see* Table 3).

Table 3. Mean Percent Change in BMD from Baseline to Endpoint[a] in Postmenopausal Women with Osteoporosis, Treated with FORTEO or Placebo for a Median of 19 Months

	FORTEO N=541	**Placebo N=544**
Lumbar spine BMD	9.7[b]	1.1
Femoral neck BMD	2.8[c]	-0.7
Total hip BMD	2.6[c]	-1.0
Trochanter BMD	3.5[c]	-0.2
Intertrochanter BMD	2.6[c]	-1.3

Ward's triangle BMD	4.2[c]	-0.8
Total body BMD	0.6[c]	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

[a] Intent-to-treat analysis, last observation carried forward.
[b] $p<0.001$ compared with placebo.
[c] $p<0.05$ compared with placebo.

FORTEO treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated. Seventy-two percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.

Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and FORTEO groups, respectively.

Bone Histology

The effects of teriparatide on bone histology were evaluated in iliac crest biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D and teriparatide 20 or 40 mcg/day. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with teriparatide was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

14.2 Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis

The safety and efficacy of once-daily FORTEO, median exposure of 10 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis (FORTEO 20 mcg, n=151). All men received 1000 mg of calcium and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD.

FORTEO increased lumbar spine BMD in men with primary or hypogonadal osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. FORTEO was effective in increasing lumbar spine BMD regardless of age, baseline rate of bone turnover, and baseline BMD. The effects of FORTEO at additional skeletal sites are shown in Table 4.

FORTEO treatment for a median of 10 months increased lumbar spine BMD from baseline in 94% of men treated. Fifty-three percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 14% gained 10% or more.

Table 4. Mean Percent Change in BMD from Baseline to Endpoint[a] in Men with Primary or Hypogonadal Osteoporosis, Treated with FORTEO or Placebo for a Median of 10 Months

	FORTEO N=151	**Placebo N=147**
Lumbar spine BMD	5.9[b]	0.5
Femoral neck BMD	1.5[c]	0.3
Total hip BMD	1.2	0.5
Trochanter BMD	1.3	1.1
Intertrochanter BMD	1.2	0.6
Ward's triangle BMD	2.8	1.1
Total body BMD	0.4	-0.4
Distal 1/3 radius BMD	-0.5	-0.2
Ultradistal radius BMD	-0.5	-0.3

[a] Intent-to-treat analysis, last observation carried forward.
[b] $p<0.001$ compared with placebo.
[c] $p<0.05$ compared with placebo.

14.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis

The efficacy of FORTEO for treating glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO. In the FORTEO group, the baseline median glucocorticoid dose was 7.5 mg/day and the median duration of glucocorticoid use was 1.5 years. The mean (SD) baseline lumbar spine BMD was 0.85 ± 0.13 g/cm^2 and lumbar spine BMD T-score was –2.5 ± 1 (number of

standard deviations below the mean BMD value for healthy adults). A total of 30% of patients had prevalent vertebral fracture(s) and 43% had prior non-vertebral fracture(s). The patients had chronic rheumatologic, respiratory or other diseases that required sustained glucocorticoid therapy. All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

Because of differences in mechanism of action (anabolic vs. anti-resorptive) and lack of clarity regarding differences in BMD as an adequate predictor of fracture efficacy, data on the active comparator are not presented.

Effect on Bone Mineral Density (BMD)

In patients with glucocorticoid-induced osteoporosis, FORTEO increased lumbar spine BMD compared with baseline at 3 months through 18 months of treatment. In patients treated with FORTEO, the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck ($p<0.001$ all sites). The relative treatment effects of FORTEO were consistent in subgroups defined by gender, age, geographic region, body mass index, underlying disease, prevalent vertebral fracture, baseline glucocorticoid dose, prior bisphosphonate use, and glucocorticoid discontinuation during trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

The FORTEO delivery device (pen) is available in the following package size:

- 2.4 mL prefilled delivery device NDC 0002-8400-01 (MS8400).

16.2 Storage and Handling

- The FORTEO delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times.
- Recap the delivery device when not in use to protect the cartridge from physical damage and light.
- During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator.
- Do not freeze. Do not use FORTEO if it has been frozen.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Potential Risk of Osteosarcoma and Voluntary FORTEO Patient Registry

Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

17.2 Orthostatic Hypotension

FORTEO should be administered initially under circumstances where the patient can immediately sit or lie down if symptoms occur. Patients should be instructed that if they feel lightheaded or have palpitations after the injection, they should sit or lie down until the symptoms resolve. If symptoms persist or worsen, patients should be instructed to consult a physician before continuing treatment *[see Warnings and Precautions (5.7)]*.

17.3 Hypercalcemia

Although symptomatic hypercalcemia was not observed in clinical trials, physicians should instruct patients taking FORTEO to contact a health care provider if they develop persistent symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness).

17.4 Other Osteoporosis Treatment Modalities

Patients should be informed regarding the roles of supplemental calcium and/or vitamin D, weight-bearing exercise, and modification of certain behavioral factors such as cigarette smoking and/or alcohol consumption.

17.5 Use of Delivery Device (Pen)

Patients and caregivers who administer FORTEO should be instructed on how to properly use the delivery device (refer to *User Manual*), properly dispose of needles, and be advised not to share their delivery device with other patients. The contents of the delivery device should NOT be transferred to a syringe.

Each FORTEO delivery device can be used for up to 28 days including the first injection from the delivery device. After the 28-day use period, discard the FORTEO delivery device, even if it still contains some unused solution.

17.6 Availability of Medication Guide and User Manual

Patients should read the *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

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